Structure-based drug design with equivariant diffusion models

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Abstract

Structure-based drug design (SBDD) aims to design small-molecule ligands that bind with high affinity and specificity to pre-determined protein targets. Generative SBDD methods leverage structural data of drugs with their protein targets to propose new drug candidates. However, most existing methods focus exclusively on bottom-up de novo design of compounds or tackle other drug development challenges with task-specific models. The latter requires curation of suitable datasets, careful engineering of the models and retraining from scratch for each task. Here we show how a single pretrained diffusion model can be applied to a broader range of problems, such as off-the-shelf property optimization, explicit negative design and partial molecular design with inpainting. We formulate SBDD as a three-dimensional conditional generation problem and present DiffSBDD, an SE(3)-equivariant diffusion model that generates novel ligands conditioned on protein pockets. Furthermore, we show how additional constraints can be used to improve the generated drug candidates according to a variety of computational metrics. This work applies diffusion models to conditional molecule generation and shows how they can be used to tackle various structure-based drug design problems